

.ETHYLENE-CARBOXYL COPOLYMERS AS DRUG DELIVERY MATRICES

BACKGROUND OF THE INVENTION

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The present invention relates to a drug delivery matrix coating, to an implantable device comprising the drug delivery matrix coating, to a method for making the drug delivery matrix coating and to a method for applying the drug delivery matrix coating to a stent.

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Stents are typically implanted within a vessel in a contracted state and expanded when in place in the vessel in order to maintain patency of the vessel to allow fluid flow through the vessel. Typically, implantation of such stents is accomplished by mounting the stent on the balloon portion of a catheter, positioning the stent in a body lumen, and expanding the stent to an expanded state by inflation of a balloon within the stent. The stent can then be left in place by deflating the balloon and removing the catheter.

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Because of the mechanical strength that is required to properly support vessel walls, stents are typically constructed of metallic materials. However, it is frequently desirable to provide localized pharmacological treatment of a vessel at the site being supported by the stent. It is convenient to employ the stent as a vehicle for drug delivery. The metallic materials are not capable of carrying and releasing drugs. Polymeric materials capable of absorbing and releasing drugs typically do not fulfill the structural and mechanical requirements of a stent, especially when the polymeric materials are loaded with a drug, since drug loading of a polymeric material diminishes the structural and mechanical properties of the polymeric material. Since it is often useful to provide localized therapeutic pharmacological treatment of a vessel at the location being treated with the stent, it is desirable to combine such polymeric materials with existing stent structures to provide a stent with the capability of absorbing therapeutic drugs or other agents, for placement and release of the therapeutic agents at a specific intravascular site.

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One solution historically used has been coating a stent's metallic structure with a polymeric material in order to provide a stent capable of both supporting adequate mechanical loads as well as delivering drugs. Techniques typically used to join polymers to metallic stents include dipping, spraying and conforming processes. However, these techniques have tended to introduce other problems into the stent products. Other problems with drug delivery matrix coatings include marginal adhesion to a substrate such as a metal substrate, insufficient elongation of the coating resulting in cracks, and limited and sub-optimal solvent choices that result in difficult application of the coating and poor manufacturability.

SUMMARY OF THE INVENTION

The present invention relates to a copolymer of carboxylic acid in a layer as applied in a drug releasing implant. The carboxylic acid copolymer may be in a matrix having a drug or in a primer or in a diffusion barrier.

One embodiment of the present invention includes a drug delivery coating. The drug delivery coating comprises a matrix comprising one or more copolymers of ethylene comprising carboxylic acid containing unsaturated monomers. The drug delivery coating also includes a drug contacting the matrix. The drug delivery coating has a strong adhesion due to Van der Waals interaction resulting from carboxylic acid bonding of the coating to the material being coated.

One other embodiment of the present invention includes a stent. The stent comprises a tubular main body. The stent also comprises a coating that is adhered to the tubular main body. The coating comprises one or more copolymers of ethylene wherein the copolymers include a carboxylic acid moiety. The carboxylic acid moiety comprises one or more of acrylic acid, methacrylic acid, maleic acid, itaconic acid and all combinations and esters of these monomers. The coating deforms to a degree that accommodates stent deformation and, as a result, is resistant to cracking and delamination. The coating adheres to stents comprised of materials such as stainless steel.

Another embodiment of the present invention includes a drug delivery system. The drug delivery system comprises a tubular main body and a first coating that overlays the tubular main body. A drug is incorporated into the first coating. A coating comprising one or more co-polymers of ethylene with a carboxylic acid moiety overlays the first coating. The carboxylic acid moiety is one or more of acrylic acid, methacrylic acid, maleic acid, itaconic acid and all combinations and esters of these monomers. For some embodiments, the first coating is biodegradable.

Another embodiment of the present invention includes a method for improving manufacturability of a drug delivery system used with a medical device. The method comprises providing a medical device with a main body and providing a coating comprising a cross-linkable co-polymers of ethylene with carboxylic acid. The method also includes applying the coating to the main body of the medical device.

The drug delivery coating of the present invention adheres to a metal substrate and has an elongation comparable to a metal or polymeric substrate. The drug delivery coating is soluble in a ternary blend. The ternary blend eases application of the coating to a medical device surface, such as a stent. The ternary blend also improves manufacturability as compared to polymeric drug delivery systems not using the ternary blend.

DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates a perspective view of one embodiment of the stent of the present invention.

Figure 2 illustrates a cross-sectional view of one embodiment of the drug delivery matrix of the present invention, wherein a drug is positioned within a polymeric matrix.

Figure 3a illustrates a cross-sectional view of another embodiment of the drug delivery matrix of the present invention wherein a polymeric matrix overlays a drug-containing matrix.

Figure 3b illustrates a cross-sectional view of another embodiment of the drug delivery matrix of the present invention wherein the polymeric matrix overlays the drug-containing matrix.

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DETAILED DESCRIPTION

One embodiment of the present invention comprises an array of matrix drug delivery coatings 42 usable as drug delivery coatings for stents 40, namely metal stents and polymeric stents, such as are illustrated, in one embodiment, in Figure 1. While a roll is shown in Figure 1, it is understood that the coating may be a sheath or a thin coat for other implant embodiments. The array of matrix coatings comprises one or more cross-linkable co-polymers of ethylene, $-(C_2H_4)-$ that comprises one or more carboxylic acid moieties. The carboxylic acid moieties are, for some embodiments, unsaturated monomers or unsaturated co-monomers. The unsaturated monomers or co-monomers are one or more of acrylic acid, methacrylic acid, maleic acid, itaconic acid and all combinations and esters of these monomers.

The carboxylic acid co-monomer content is at least about 5% by weight and not more than about 50% by weight of the polymer. The carboxylic co-monomer content is, for some embodiments, in a range of about 15 to 40% by weight of the polymer. The acid groups are, for some embodiments, partially neutralized. For other embodiments, the acid groups are fully neutralized using sodium hydroxide, potassium hydroxide, ammonia, and the like.

The term "ionomers" as used herein refers to polymers with acid groups that are neutralized with metal cations.

The term "matrix polymer" as used herein refers to a polymer capable of forming a coating on a surface of a medical apparatus and providing a network for containing a drug. The matrix polymer has functional moieties capable of crosslinking by hydrogen bonds to other moieties within the matrix polymer and crosslinking to any other moieties derived from the medical apparatus to enhance the strength and

toughness of the coating. Adhesion is enhanced by Van der Waals interaction resulting from carboxylic acid bonding of the coating to the medical apparatus.

The term "elongation" as used herein refers to a percent elongation to break or an amount of strain the polymer can endure before rupturing.

5 Another embodiment of the present invention includes the matrix drug delivery coating of the present invention and a drug. For some embodiments, such as is illustrated at 20 in Figure 2, the polymer comprising the coating acts as a drug eluting matrix. The drug 22 is incorporated within the drug eluting matrix 24. For some embodiments, the drug is a particulate which is dispersed within the drug eluting matrix
10 24. For other embodiments, the drug is dissolved within the matrix 24.

 The drug delivery coating acts as a barrier to rapid diffusion of the drug through the coating and to a treatment site. The drug delivery coating has a thickness ranging from about 0.1 to 3.0 mils, when applied to a stent. Because diffusion and drug release are delayed by the coating, the coating is usable for releasing drugs to a
15 treatment site after a time interval of no or negligible drug release.

 The coating of the present invention is usable with multiple drug delivery matrices in order to orchestrate drug release. In one embodiment, the coating, as shown in cross-section in Figure 2, overlays a surface 26, such as a stent surface. With this embodiment, the coating functions as a drug release coating. For another embodiment
20 which is not shown, the coating is drug free and does not function as a drug release coating.

 For some embodiments, the coating made with co-polymers of ethylene is a primer layer or a diffusion barrier. As a primer layer, the coating adheres to the surface of a stent. The primer layer also has functional moieties for crosslinking to a
25 matrix polymer. For some embodiments, the primer layer is a dispersion of ethylene acrylic acid (EAA), such as Primacor 5980, available from Dow-Corning Corp. in Midland, Michigan or MICHEMPRIME 4983R, available from Michelman of Cincinnati, Ohio, or which is a dispersion that is capable of providing carboxyl moieties to the surface. As a primer layer, the coating of the present invention deforms to a

degree that accommodates stent deformation, such as stent strut deformation. As a result, the coating is resistant to cracking and delamination and provides both elongation and high adhesion. For some embodiments, a drug is incorporated in the primer or the diffusion barrier. Typically, the drug concentration for these embodiments is lower if the matrix layer is present.

Thus, the coating of the present invention accomplishes what many other polymers cannot perform. Thermosets such as epoxies, polyesters, phenolics, polyimide, as well as conventional thermoplastics such as vinyl chloride, cellulotics, styrene, methyl methacrylate and thermoplastics such as PEEK, PPS, polysulfone, polycarbonate, Mylar, unless the strain occurs above the polymer's glass transition temperature, do not elongate and adhere to a degree that makes them acceptable coatings for stent devices.

For other embodiments, the polymer comprising the coating is positioned to provide a diffusion limiting barrier for a drug reservoir, such as a micro-depot 17, shown in Figure 3a. The micro-depot 17 is defined by a divot formed at the surface 14 of the stent 13. This embodiment is illustrated generally at 10 in Figure 3a. A coating illustrated at 12 overlays a stent surface 14. For some embodiments, the coating 12 includes drugs and for other embodiments, the coating 12 is drug-free. The polymer overcoat 16 of the present invention overlays the coating 12. The coating matrix includes one or more of poly(ethylene-acrylic acid), EAA, poly(ethylene-vinyl alcohol), poly(ethylene vinyl acetate), poly n-butyl methacrylate, poly(ethylene oxide) or a polyurethane elastomer such as Bionate 80A, manufactured by Polymer Technology Group of Berkeley, California. Bionate 80 is a polycarbonate-urethane and is a thermoplastic elastomer formed as a reaction product of a hydroxyl terminated polycarbonate, an aromatic diisocyanate, and a low molecular weight glycol which is used as a chain extender. The overcoat 16 includes one or more of EAA, ethylene-methacrylic acid (EMAA), and other ethylene, acrylic acid-based materials.

For other embodiments such as is illustrated at 30 in Figure 3b, the polymer overcoat 16 functions as a cover over a drug-only layer 32 or a drug/non-drug

mixture layer, which is not shown. The coat may be biodegradable but there may be non-biodegradable coats, as well. One layer of this type is a layer that comprises a drug and a biodegradable material such as phosphatidylcholine. Other suitable biodegradable materials include linear aliphatic polyesters like polyglycolide and polylactide from poly(alpha-hydroxyacetic acids), poly(orthoesters), polyanhydrides, polysaccharides, poly(ester amides), tyrosine-based polyarylates or polyiminocarbonates or polycarbonates, poly(D,L-lactide-urethane), poly(beta-hydroxybutyrate), poly(e-caprolactone), poly[bis(carboxylatophenoxy) phosphazene], poly(amino acids), pseudo-poly(amino acids), and copolymers derived from amino acids and non-amino acids. As the biodegradable layer degrades, the drug is released.

For other embodiments, the matrix polymer coats a medical device such as a stent as shown at 40 in Figure 1 but the polymer acts as a primer, and is free of drugs. For these embodiments, the matrix polymer 42 coats surfaces that are regarded as difficult to coat, such as stainless steel. Stainless steel is regarded as a difficult to coat metal because stainless steel has an outer surface that is trivalent chromium oxide, which provides a less reactive surface than other metal oxides. It is the interaction between metal oxides on the substrate and functional groups on the polymer that provide the adhesive force.

For some embodiments, the polymer coating formulation of the present invention also includes one or more of a surfactant, a colorant, and one or more plasticizers or mixtures of these materials. Some of the co-polymer coating embodiments of the present invention comprise co-polymers that are soluble in ternary blends comprising toluene, a chlorinated solvent, and a lower alcohol. The ternary blends of toluene, chlorinated solvents, and lower alcohols, are usable to dissolve and to apply the polymer or polymer/drug blend to a stent. For example, a blend of 15% trichloroethane, 15% 2-propanol and 70% toluene is usable to dissolve a coating polymer manufactured by Dow Chemical, PRIMACOR 5980. For some embodiments, the polymer coating formulation is dissolved at an elevated temperature. The use of

these ternary blends renders the coating application process easier in that a coating has a viscosity that eases application and uniformity of thickness.

Specifically, solvents dissolve the polymer to make a coating solution. Surfactants are added to improve substrate wetting. Surfactants are also added to prevent foaming. Plasticizers increase elongation at the expense of hardness and tensile strength.

The co-polymers are neutralized in a volatile or a non-volatile base. The copolymers are dispersed in water and in co-solvents such as the ternary blends that are described. Specifically, the co-solvents include the ternary blends of toluene, chlorinated solvents and lower alcohols.

In one particular example, a coating of the present invention is made with a PRIMACOR 5980I, which is manufactured by Dow Chemical of Midland, Michigan. The PRIMACOR 5980I is an ethylene acrylic acid copolymer, EAA, that adheres to metals and other polar substrates. The PRIMACOR 5980I has the physical properties described in Table 1.

Table 1

	Physical Properties	Test Method	Values (SI)
20	Resin Properties		
	Weight Percent Comonomer	Dow Method	20.5
	Melt Index, g/10 min	ASTM D 1238	300
	Melt Flow Rate, g/10 min	ASTM D 1238	13.8
	Density, g/cc	ASTM D 792	0.958
25	DSC Melting Point, F (C)	Dow Method	171 (77)
	Vicat Softening Point, F(C)	ASTM D 1525	108 (42)
	Molded Part Properties		
	Ultimate Tensile, psi (Mpa)	ASTM D 638	1400 (10)

Ultimate Elongation, %	ASTM D 638	390
Tensile Modulus, 2% secant, psi(MPa)	ASTM D 638	4800(33)
Hardness, Shore D	ASTM D 2240	50

5 One other polymer formulation usable in the coating formulation of the present invention is provided in an ammonia neutralized aqueous dispersion at 25% solids, manufactured by Michelman Inc. The product name is Michem Prime 4983R. The Michem Prime 4983R product includes EAA solids in a percent of 25% non-volatiles. Dow Primacor 5980i is also usable. The specific gravity is 0.98 to 1.00. The
10 particle size is about 0.03 micron. The viscosity is about 50 to 400, as measured with a No. 2 spindle. The hardness, as measured by ASTM test D-5, is about 54 sd.

 This Michem Prime 4983R dispersion is, for some embodiments, blended in a concentration that is less than 40% w/w, and is preferably within a range of 5 to 20% w/w with a co-solvent and, optionally, with a drug component. This
15 dispersion is applied by standard coating application techniques such as spray coating or dipping, at substantially room temperature. When used as a primer, an addition of about 20 to 50 micrograms of coating material per stent is typically used. As a matrix with drug, about 50 to 500 micrograms per stent are applied to each stent. If used as a diffusion limiting barrier coat, a quantity of about 50 to 500 micrograms of material are
20 applied to each stent. Once the coating is applied to a stent, the coating and stent are baked at low temperature, 120 degrees to 150 degrees F, for a period of time that is sufficient to drive off the solvents and any volatile amine. Coating and heating produces a conformal coating on the device. For some embodiments, the coating is dried at room temperature, rather than being subjected to baking.

25 Another embodiment of the present invention includes a stent or other implantable medical device made with the coating of the present invention. The medical device comprises a main body comprising a material such as stainless steel, nickel, gold, chrome, nickel titanium alloy, platinum, other metals, silicone, polyethylene, other polyolefins, polyesters, other plastics, glass, polyurethane, acetal,

polyamide, and polyvinyl chloride. Medical devices include catheters, microcatheters, wires, wound drains and dressings, arteriovenous shunts, gastroenteric tubes, urethral inserts, laparoscopic equipment, pellets and implants. The medical devices are made for some embodiments with coating alone. For other embodiments, the medical devices
5 deliver drugs through the drug delivery coating.

The drug delivery coating of the present invention substantially eliminates problems of marginal substrate adhesion, insufficient elongation resulting in cracks and limited and sub-optimal solvent choices resulting in difficult application and poor manufacturability. The carboxylic acid groups of the ethylene polymer impart a
10 high adhesion to the coating so that the coating strongly adheres to metal. The ethylene content insures sufficient elongation of the coating to accommodate the strain associated with stent expansion.

An ability to neutralize the acid groups with a volatile or permanent counter ion provides water dispersibility properties to the coating. The water
15 dispersibility is compatible with organic co-solvents such as 2-propanol or methyl ethyl ketone to aid in substrate wetting and improved application properties. The acid groups that are not ionically neutralized in the dried film are usable to associate with amine groups on a drug, such as Actinomycin D, and to retard its release.

Thus, the drug delivery coating of the present invention resists wet
20 abrasion. The coating remains coherent without cracks despite flexing when applied to substantially inert surfaces that are difficult to coat, such as stainless steel. This performance is an improvement over other coatings which do not display optimal properties when applied to stainless steel.

Due to a high ethylene content, the hydrophobic nature of the dry film
25 retards the transport of drug molecules, which tend to be functionalized and have some hydrophilic character.

Examples of such active ingredients include antiproliferative substances as well as antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antioxidant, and combinations thereof. A suitable

example of an antiproliferative substance includes actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich 1001 West Saint Paul Avenue, Milwaukee, WI 53233; or COSMEGEN available from Merck). Synonyms of actinomycin D include actinomycin, actinomycin IV, actinomycin I1, actinomycin X1, and actinomycin C1. Examples of suitable antineoplastics include paclitaxel and docetaxel. Examples of suitable antiplatelets, anticoagulants, antifibrins, and antithrombins include sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin; vapiprost, prostacyclin and prostacyclin analogs, dextran, D-phe-pro-arg-chloro-methylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocore). Examples of suitable antimitotic agents include methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin, and mutamycin. Examples of suitable cytostatic or antiproliferative agents include angiopeptin (a somatostatin analog from Ibsen), angiotensin converting enzyme inhibitors such as CAPTOPRIL (available from Squibb), CILAZAPRIL (available from Hoffman-LaRoche), or LISINOPRIL (available from Merck); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonist, LOVASTATIN (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck), monoclonal antibodies (such as PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available form Glazo), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, and dexamethasone.

While the foregoing therapeutic agents have been used to prevent or treat restenosis, the drugs are provided by way of example and are not meant to be limiting, since other therapeutic drugs may be developed which are equally applicable for use in

the present invention. The treatment of diseases using the therapeutic agents described as well as dosage rates are known.

For some embodiments, a selected drug is intimately mixed with the polymeric coating material of the present invention in order to uniformly disperse the therapeutic drug in the polymeric material. For other embodiments, the drug is incorporated into a matrix such as a biodegradable polymer matrix. The specific method of uniformly dispersing the therapeutic drug in the polymer is variable, and depends upon the stability of the therapeutic drug to thermal processing. Ethylene and acrylic acid, for example, are co-polymerized by free radical techniques to form an essentially linear polymer. However, ethylene is not "crosslinked" by the acid co-polymer. The acid groups randomly placed along the chain hydrogen bond to each other. The acid groups crosslink each other, not the ethylene groups.

For some embodiments, the therapeutic drug is uniformly dispersed in the polymeric material by coextruding small solid particles of the drug with the polymer material. The specific method of uniformly dispersing the therapeutic drug in the polymer varies and depends upon the stability of the therapeutic drug to thermal processing. The therapeutic drug is uniformly dispersed in the polymeric material by coextruding small solid particles of the selected therapeutic drug with the selected polymeric material. This extrusion device includes a hopper into which the polymeric material and small particles of selected therapeutic drug are added together, and into which a porosigen is also added, if desired. The extruder also typically includes a lead screw that drives and that intimately mixes the ingredients together, to uniformly disperse the small particles of the therapeutic drug, and if desired, a porosigen as well, in the polymeric material.

The barrel of the extruder is heated by temperature controlled heaters surrounding the barrel in stagers. A motor and associated gears are provided to drive the lead screw, and a cooling system is also typically provided. This method of intimately mixing the therapeutic drug and polymeric material yields a relatively high and uniformly distributed loading of the therapeutic drug in the polymer. While a

loading of the therapeutic drug is currently no more than about 40% by weight, depending upon the specific application and interaction of the polymer with the drug, drug loadings as high as 70% by weight have been achieved by this method. A preferable concentration range is 5 to 20% by weight. The drug loaded polymer is extrudible into an appropriate shape, or can be subsequently calendered to produce a drug loaded polymer film having a smooth surface, with the therapeutic drug uniformly distributed in the film.

A polycarbonate-urethane material such as Bionate 80 is very hygroscopic. Pellets of Bionate 80 are dried by a process such as forced air dehumidifying dryer at 82 degrees C. For at least about 4 hours prior to extrusion or injection molding. Bionate 80 pellets are typically filtered during extrusion, though filters such as a 350 mesh filter and two 500 mesh filters.

Extrusion equipment is set with a cross head temperature of about 200 degrees C to 215 degrees C to initiate the flow. Once flow is established, the cross head temperature is decreased until steady, viscous flow is achieved. Extrusion conditions for the polycarbonate-urethane material are typically within the following ranges:

Conditions	Temperature (C)	Temperature (F)
Barrel-Zone 1	200-215	390-420
Barrel-Zone 2	193-230	380-445
Barrel-Zone 3	193-230	380-445
Die	200-215	390-420
Melt Temperature	191-221	375-430

Extruder Configuration

Parameter	Value
Length to Diameter Ratio	24:1

Compression Ratio	2.5:1 to 3.5:1
Cooling Water Temperature	18-20 degrees C.

5 The particles of the desired therapeutic drug are formed to have a maximum cross-sectional dimension of about 10 microns. An average particle size of less than 10 microns and a uniform distribution of the particles of the therapeutic drug in the polymeric material provide a therapeutically effective amount of the therapeutic drug in the layer of the polymeric material to be applied to the structure of the stent, since the layer of polymeric material typically is as thin as 25 microns. The size and
10 distribution of the particles of the therapeutic drug affect the physical properties of the polymer.

15 In other embodiments, the therapeutic drug is compounded with the polymer by calendering the ingredients, such as in a two roll mill, for example. This method yields a relatively high and uniformly distributed loading of the therapeutic drug in the polymer.

20 The matrix coating is applicable to the surface of a stent using methods such as dipping, spraying, flowing, rolling and brushing. Thickness of the coating ranges from about 0.1 to about 3 mils. The thickness is adjustable by adjusting viscosity of the coating material prior to application. Thickness is also adjustable by
20 applying multiple coating layers.

25 The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present invention. Modifications and variations of the above-described embodiments of the invention are possible without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.